Comments on

National Toxicology Program
Draft Background Document on
Glass Wool Fibers

For Presentation at the NTP Report on Carcinogens,
Expert Panel Meeting
Research Triangle Park, NC
June 8-10, 2009

by

Gary M. Marsh, Ph.D., F.A.C.E.
Professor and Interim Chair
Director, Center for Occupational Biostatistics and Epidemiology

with assistance from

Jeanine M. Buchanich, Ph.D.
Research Assistant Professor of Biostatistics
Deputy Director, Center for Occupational Biostatistics and Epidemiology

Ada O. Youk, Ph.D.
Research Assistant Professor of Biostatistics
Deputy Director, Center for Occupational Biostatistics and Epidemiology

Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh

130 DeSoto Street
Pittsburgh, PA 15261

Phone: 412-624-3032
Fax: 412-624-9969
Email: gmarsh@cobe.pitt.edu

North American Insulation Manufacturers Association – Sponsoring Organization

May 22, 2009

Introduction

My name is Gary Marsh. I received my Ph.D. in Biostatistics in 1977 from the University of Pittsburgh, Graduate School of Public Health, and in 1997 became a Fellow of the American College of Epidemiology. Currently, I am Professor and Interim Chairman of the Department of Biostatistics and Director of the Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. I have devoted my 32-year research-oriented career at the University of Pittsburgh to methodological development and field applications in the areas of occupational biostatistics and epidemiology.

I have designed and directed more than 50 research occupational health studies and published more than 200 peer-reviewed articles, book chapters and other documents. My professional service as an occupational biostatistician/epidemiologist includes membership on the National Institute for Occupational Safety and Health (NIOSH) Safety and Occupational Health Study Section (1988-92), the International Agency for Research on Cancer (IARC) Working Group to evaluate the carcinogenicity of man-made vitreous fibers (2001) and the U.S. Environmental Protection Agency, Science Advisory Board, Asbestos Panel (2008).

I am pleased to present, on behalf of the North American Insulation Manufacturer's Association (NAIMA), the following comments in support of the National Toxicology Program's (NTP) consideration of delisting glass wool (respirable size) from the upcoming *12th Report on Carcinogens*. My comments include an overview and comparison of key findings from the U.S. cohort study of FG workers as well as the concurrent cohort studies of FG workers conducted in Europe and Canada. I also provide a critical evaluation of the epidemiology and other relevant studies published since the IARC's 2001 decision that "glass wool insulation" was not classifiable as to its carcinogenicity in humans. I concluded from this evaluation that IARC's 2001 decision to downgrade glass wool insulation from Group 2B to Group 3 remains valid in light of the additional epidemiological evidence provided by the post-2001 studies.

Relevance and Significance of Comments

My comments in support of the National Toxicology Program's (NTP) consideration of delisting glass wool from the upcoming *12th Report on Carcinogens* reflect my 26-year experience at the University of Pittsburgh as Co-investigator (1975-86) and Principal Investigator (1987-2001) of the NAIMA-sponsored historical cohort study of U.S. man-made vitreous fiber production workers. The U.S. cohort study, which comprised 32,110 workers (935,581 person-years) potentially exposed to glass wool or glass filaments (5,431 glass filament only) during the 47-year 1946 to 1992 observation period, remains by far the largest and most comprehensive epidemiology study of glass wool or filament workers ever conducted. As such, the U.S. cohort study represented a substantial portion of the epidemiological evidence that IARC relied upon in 2001 to downgrade the classification of glass wool insulation from Group 2B to Group 3 (IARC, 2002), and now in 2009, the U.S. cohort study represents a substantial portion of the epidemiological data that NTP will rely upon as they consider delisting glass wool from the *12th Report on Carcinogens*.

The comments provided below are organized as follows:

Background and Key Findings of U.S. Cohort Study

Between 1975 and 2001, the University of Pittsburgh, Graduate School of Public Health, Department of Biostatistics (UPitt) conducted a large and comprehensive, historical cohort study of production and maintenance workers from 10 of the oldest and largest fiber glass wool and/or glass filament (termed "fiber glass" (FG)) manufacturing plants in the U.S. The U.S. cohort study was prompted by concern about the safety of FG that arose from observations that these fibers produced cancer when implanted into laboratory animals (Stanton and Wrench, 1972), and that these fibers can be inhaled and retained within the human respiratory system. Thus, while our study evaluated mortality patterns for many malignant and non-malignant cause of death categories, we focused on chronic diseases of the respiratory system.

The Original U.S. Cohort

The original U.S. FG cohort comprised 14,815 male workers with at least one year of work experience in production or maintenance during the years 1945 to 1963 in one or more of 10 plants (originally 11 plants but 2 plants combined in later updates). Exceptions included a 6-month employment criterion for two plants (Plant Nos. 6 and 10) that produced small-diameter fibers (< 1.5 μm). Two of the plants produced only glass filament (Plant Nos. 2 and 5) and a total of four plants also made small diameter (< 1.5 μm) glass or quartz microfibers for special applications (Plant Nos. 1, 6, 9, 10). The original cohort was follow-up initially until 1977 (Enterline et al., 1983; Enterline and Marsh, 1984).

In 1987, we reported the results of a 1982 follow-up including a nested case-control study of respiratory disease mortality that enabled some control for cigarette smoking. In 1990, we reported our last (1985) update of the original cohort that included Poisson regression modeling of standardized mortality ratios for respiratory system cancer (RSC) in relation to several FG exposure metrics. The FG exposure estimates used in the original U.S. cohort study were developed at the University of Pittsburgh by Drs. Nurtan Esmen and Morton Corn and coworkers (Esmen et al., 1978; 1979; Esmen et al., 1982).

The Expanded and Enhanced U.S. Cohort

Because the 1985 and earlier updates of the original U.S. cohort were limited by incomplete data on race and work history and a total absence of data on female employees and exposures to workplace contaminants other than fibers, a comprehensive mortality surveillance program for the U.S. cohort was initiated at the University of Pittsburgh under my direction in 1987. This program, sponsored by NAIMA, involved a complete re-enumeration and enlargement of the original cohort to include female employees, workers employed after the original 1963 cohort end date (through 1978), and workers from additional manufacturing sites. We also made efforts to characterize more completely the work histories, racial composition, and smoking patterns of the cohort. The surveillance program included ongoing mortality follow-up, a new nested case-control study of RSC among male workers, a probability sample-based survey to characterize smoking patterns for the U.S. cohort and a detailed evaluation of mesothelioma mortality.

In addition, in 1988, NAIMA initiated a new exposure assessment project at the University of Massachusetts at Worcester (then moved to the Harvard School of Public Health and the University of Massachusetts at Lowell) under the direction of Drs. Thomas Smith and Margaret Quinn. This project provided for each of the 10 FG plants, comprehensive historical data on respirable fiber exposures and on exposures to several co-exposures (arsenic, asbestos, asphalt, epoxy, formaldehyde, polycyclic aromatic hydrocarbons, phenolics, silica, styrene and urea).

In 2001, we completed the first (1992) update of the expanded and enhanced U.S. cohort and published our findings in a series of eight peer-reviewed articles comprising the September 2001 edition of the *Journal of Occupational and Environmental Medicine.* (Buchanich et al., 2001; Marsh et al., 2001a, 2001b, 2001c; Quinn et al., 2001; Smith et al., 2001; Stone et al., 2001; Youk et al., 2001). As noted above, the eight *JOEM* articles on the 1992 update of the U.S. cohort provided a significant portion of the epidemiological data that IARC relied upon in 2001(IARC, 2002) and that NTP will rely upon as they consider delisting glass wool. The following section provides an overview of the key findings taken from the 1992 update of the U.S. cohort.

Key Findings of the U.S. Cohort Study

Methodology: Subjects were 32,110 workers employed one year or more during 1945-78 at any of 10 U.S. FG manufacturing plants, including 10,961 who produced mostly glass wool, 15,718 who produced glass wool and filament and 5,431 who produced only filament (Table 1).

Table 1. Plants and Products Included in U.S. Cohort Study (Marsh et al., 2001a)

Study Plant No.	Location	Principal FG Product	Beginning of Production	Latest Work History	No. of Workers
1	Parkersburg, WV	Mostly wool [a.]	1952	1987	1,032
4	Kansas City, KS	Mostly wool	1946	1987	3,692
6	Santa Clara, CA	Mostly wool [a.]	1945	1987	2,680
11	Defiance, OH	Mostly wool	1945	1987	2,281
14	Shelbyville, IN	Mostly wool	1964	1987	1,276
Total mostly wool					10,961
9	Newark, OH	Wool and filament [a.]	1940	1987	9,856
10	Waterville, OH	Wool and filament [a.]	1945	1987	1,892
15	Kansas City, KS	Wool and filament	1946	1987	3,970
Total wool and filament					15,718
2	Ashton, RI	Filament only	1946	1987	2,853
5	Huntingdon, PA	Filament only	1946	1987	2,578
Total filament only					5,431
All FG workers combined					32,110

a. Special application glass or quartz microfibers (<1.5 μm) were also made at this plant

The cohort is comprised primarily of white males (83.8% of those with known race) including 5,575 (17.4%) workers of unknown race. The cohort is about evenly divided between short-term (<5 years - 47.9%) and long-term (5+ years - 52.1%) workers. 5,675 (17.7%) workers were employed for 20 or more years and 15,766 (49.1%) were followed for 30 or more years.

We identified 9,173 deaths among the FG cohort between 1946 and 1992 and determined cause of death for 9,060 (98.8%). Standardized Mortality Ratios (SMRs) and 95% confidence intervals were computed for the total FG cohort and selected subgroups using both national and local county rates. We estimated smoking prevalence in the cohort from a random sample of subjects and used this to adjust SMRs for respiratory system cancer (RSC) for confounding by cigarette smoking using the indirect method of Axelson and Steenland (1988).

Smoking history data were also obtained in a nested, matched case-control study of respiratory system cancer. We identified cases as all male study members dying from RSC during 1970-92. For each case, one control was randomly selected from among all male study members at risk during the 1970-92 time period and alive at the age the corresponding case died. Controls were also matched by date of birth (within one month), but were not matched on plant. Lifetime smoking history data were obtained for all but three subjects via structured telephone interviews with more than 80% of cases and controls (or a knowledgeable informant).

We performed relative risk regression modeling (conditional logistic regression) on 516 matched sets (631 cases and 570 controls) to examine the relationship between mortality from RSC and exposure to respirable glass fibers (RFib) and to each of the potential co-exposures, with and without adjustment for smoking history. Analyses included categorical measures of exposure to RFib and formaldehyde that were both unweighted and weighted using time lags and unlagged/lagged time windows. We also considered quantitative measures of exposure to RFib, formaldehyde and silica together in the same model with other exposures. We used fractional polynomials (Greenland, 1995) to investigate the functional form of the exposure-response relationship and addressed the statistical issues of linearity (linear splines), collinearity (orthogonal polynomials), effect modification and potential confounding by smoking, plant and co-exposures.

Results- Exposure Assessment: Potential exposures to RFib, asbestos, asphalt, formaldehyde, phenolics, silica, and urea occurred at varying levels in each of the study plants, while other co-exposures occurred in only some study plants. The median average intensity of RFib exposure computed across all individual workers was 0.035 fibers per cubic centimeter(cc), ranging from 0.001 fibers/cc for workers in one FG filament plant (Plant 5) to 0.167 fibers/cc for workers in a FG plant producing mostly wool (Plant 6). Median cumulative RFib exposure was 1.441 fibers/cc-months for all workers, ranging from 0.086 (Plant 5) to 6.382 (Plant 6) fibers/cc-months.

Results-Cohort analysis: Table 2 shows for the total cohort, observed deaths and SMRs for selected cancer sites. We observed a statistically significant 16% excess in RSC mortality based on U.S. rates that reduced to a not statistically significant 6% excess based on local county rates. A not statistically significant 11% local county rate-based excess was observed for cancers of the buccal cavity and pharynx. No statistically significant RSC excesses were observed among long-term (> 5 years employment) workers producing mostly glass wool (SMR=1.06, 95%CI=.90-1.26), glass wool and filament (SMR=1.03, 95%CI=.91-1.16) or glass filament only (SMR=0.96, 95%CI=.76-1.19). SMRs were generally higher among short-term workers (employed < 5 years) and did not appear to be related to duration of employment or the time since first employment (see Table 5 below).

Table 3 shows estimated "ever" smoking prevalence rates for male FG workers and the corresponding U.S. or state populations by plant. Also shown are local county rate-based SMRs for RSC unadjusted and adjusted for confounding by smoking. For all male FG workers, the unadjusted 7% RSC excess is reduced to a statistically significant 14% deficit with adjustment for smoking. With the exception of Plant 2, smoking-adjusted RSC SMRs are 1-33% less than their unadjusted counterparts.

Table 2. Observed Deaths and SMRs for Selected Cancer Sites, Total FG Worker Cohort, 1946-92, National and Local County Comparisons (Marsh, et al., 2001a)

Cause of Death (ICD Codes)	Total Cohort				
	OBS	SMR_N[b]	95% CI	SMR_C[b]	95% CI
All malignant neoplasms (140–209)	2,243	0.98	0.94–1.02	0.94**	0.90–0.98
Buccal cavity and pharynx (140–149)	63	1.07	0.82–1.37	1.11	0.85–1.42
Digestive organs and peritoneum (150–159)	528	0.90**	0.82–0.97	0.89**	0.82–0.97
Respiratory system (160–163)	874	1.16**	1.08–1.24	1.06	1.00–1.14
Larynx (161)	29	1.04	0.70–1.50	1.01	0.68–1.45
Bronchus, trachea, lung (162)	838	1.17**	1.09–1.25	1.07	1.00–1.14
All other (160, 163)	7	0.80	0.32–1.66	0.85	0.34–1.75
Breast (174)	50	0.70**	0.52–0.92	0.69**	0.51–0.91
Prostate (185)	122	0.81*	0.67–0.96	0.82*	0.68–0.97
Kidney (189.0–189.2)	54	1.01	0.76–1.32	0.94	0.71–1.23
Bladder and other urinary organs (188, 189.9)	64	1.14	0.88–1.45	1.07	0.82–1.37
Melanoma of skin (172.0–172.4, 172.6–172.9)	27	0.80	0.53–1.17	0.85	0.56–1.24
Central nervous system (191, 192)	50	0.78	0.58–1.03	0.82	0.61–1.08
All lymphatic and hemaopoietic tissue (200–209)	199	0.92	0.80–1.06	0.90	0.78–1.04

[a] For definition of abbreviations, see Table 5.
[b] SMR_N based on US rates, SMR_C based on corresponding local county rates.
* $P < 0.05$; ** $P < 0.01$.

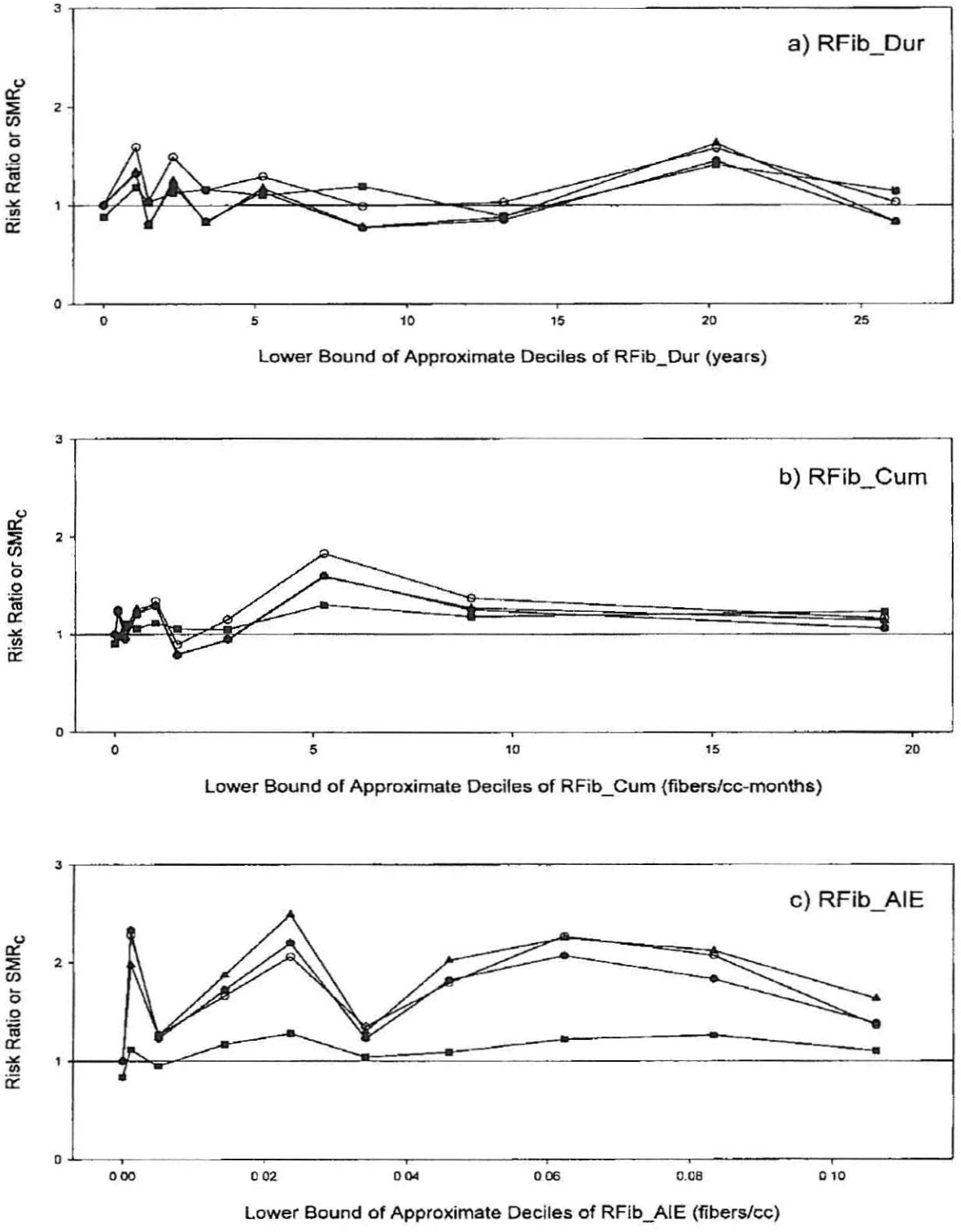
Table 3. Estimated Smoking Prevalence Rates and SMRs Unadjusted and Adjusted for Confounding by Smoking, Male Workers Only (Marsh et al., 2001f)

Plant no.[a]	Ever smoking prevalance		RSC SMR_C[b]		
	FG workers	US/state	Unadjusted	Adjusted	% Change
All FG	76.3	65.6	1.07	0.86**	–20
1	60.0	66.2	1.01	1.11	+10
2	68.4	68.1	1.18	1.17	–0.8
4	67.7	51.5	1.13	0.86	–24
5	75.0	60.5	0.85	0.69**	–19
6	71.4	56.8	1.28	1.02	–20
9	77.8	64.3	1.05	0.87**	–17
10	77.8	64.3	0.85	0.70	–18
11	79.2	64.3	1.26	1.02	–19
15	79.4	51.5	0.99	0.64**	–33

**$P < 0.01$.
[a]Plant 14 not included due to unreliable data.
[b]SMR_C based on corresponding local county rates.

Case-control Data Analysis: Among the potential confounding factors considered, "ever" cigarette smoking was a statistically significant predictor of RSC risk (odds ratio=13.2, p<.001). In models including unweighted and weighted categorical exposure measures, duration of exposure and cumulative exposure to RFib at the levels encountered at the study plants did not appear to be associated with an increased risk of RSC (Figure 1). There was some evidence of elevated RSC risk associated with non-baseline levels of average intensity of exposure to respirable glass, but when adjusted for smoking, this was not statistically significant and there was no apparent trend with increasing exposure (Figure 1).

Fig. 1. RR for RSC estimated from a case-control study, and SMR estimated from a cohort study, by approximate deciles of RFib_Dur, RFib_Cum, and RFib_AIE, with and without adjustment for smoking and plant, for male subjects from 1970 to 1992.



In the categorical exposure models, none of the other individual co-exposures encountered the study plants appeared to be associated with an increased risk of RSC. Our more extensive analysis of quantitative exposure data for RFib, formaldehyde and silica substantiated the findings from the categorical data analysis of no apparent exposure-response relationship between RSC risk and either cumulative or average intensity of exposure to RFib. We observed some evidence of increased RSC risk among workers with relatively high levels of average intensity of exposure to formaldehyde and/or silica. No positive associations were identified between RSC risk and any of the other exposures considered in the case-control study (data not shown).

Evaluation of Mesothelioma Mortality: For our mesothelioma evaluation, we manually reviewed all death certificates or National Death Index codes for any mention of the word "mesothelioma." We attempted to interview the next-of-kin of all decedents with mention of mesothelioma and to obtain medical records and tissue specimens for histo-pathology review. We also estimated the mortality risk from mesothelioma in the cohort using two cause of death categorizations that included both malignant and non-malignant codes. We found that only 10 of 9,060 death certificates or NDI codes mentioned "mesothelioma." A review of pathology specimens and/or medical records for five of the 10 workers found only one to have at least a 50% chance of being a mesothelioma. Mesothelioma mortality risks were not elevated using either classification scheme.

Conclusions from 1992 Update of U.S. Cohort Study: Our findings to date from external comparisons in the U.S. cohort study and internal comparisons in the nested case-control study suggest that exposure to RFib at the levels encountered in the study plants was not associated with an increased risk of RSC, mesothelioma or any other malignant or non-malignant cause of death category considered. These findings were generally similar to our previous 1985 follow-up of the original FG cohort, and to those of other cohort studies of FG production workers conducted as of 2001 in the U.S., Canada and Europe (Boffetta et al., 1992, 1997, 1999; Chiazze et al., 1992, 1993, 1995, 1997a, 1997b, 1999; Consonni et al., 1998; Doll, 1987; Gustavsson et al., 1992; Plato et al., 1995; Sali et al., 1999; Shannon et al., 1987, 1990; Simonato et al., 1987; Wong et al., 1991). A more detailed comparison of results from the U.S., European and Canadian cohort studies is provided in a later section of my comments.

Background and Key Findings of European Cohort Study

Since 1976, IARC has coordinated a cohort study on mortality and cancer incidence among male and female workers glass wool or glass filament production workers in six plants across five European countries. Four plants produced glass wool, one plant produced glass filament and one plant produced both products. This cohort study has resulted in a number of country-specific investigations as well as several analyses of the combined cohort.

Unlike the U.S. cohort study, the European cohort study included no direct estimates of historical respirable glass fiber exposure for individual subjects due the unavailability of work history information for the early (pre-1977) years of the study. Contemporary exposures to respirable glass fibers were measured by Cherrie et al. (1986) for four of the glass wool plants included in the in European study. The authors reported an overall range across plants of 0.01 to 1.00 fibers/cm^3, with the mean concentrations in the main production areas ranging from 0.01 to 0.05

fibers/cm^3 and in secondary production from 0.02 to 1.00 fibers/cm^3. These levels are roughly comparable to the corresponding ranges seen in the U.S. study plants.

Due to the lack of work history data, the exposure assessment for the European study was limited to the assignment of technological phases within the study plants. This analysis was done in a non-time dependent fashion, with workers assigned and fixed to the phase within which their date of first employment occurred. This analysis assumed that airborne exposure levels to glass fibers (and ostensibly subject's exposures) decreased with increasing technological phase. Also, unlike the U.S. cohort study, no information on potentially confounding exposures such as smoking or other co-exposures was available.

The following summary is limited to the latest findings for glass wool from the combined cohort mortality and incidence studies and the nested case-control study of lung cancer in one plant, as these were (are) most relevant to IARC's 2001 downgrading of insulation glass wool (IARC, 2002) and NTP's consideration of delisting of glass wool (Boffetta et al., 1997; Boffetta et al., 1999; Gardner et al., 1988). A later section of my comments provides a comparison of the key features and findings from the U.S., European and Canadian cohort studies.

Combined Mortality Study

Boffetta et al. (1997) studied 8,335 workers exposed to glass wool from five plants and 3,559 workers from two plants exposed to glass filament (Table 4). Mortality follow-up was through 1990 or 1992 depending on the subcohort. For 6,936 glass wool workers with one or more years of employment, the authors observed a statistically significant excess of cancers of the bronchus, trachea and lung (lung cancer) based on national reference rates (140 deaths, SMR=1.27, 95%CI=1.07-1.50) [1]. This excess was reduced to a not statistically significant 12% level when national rates were adjusted for local factors (140 deaths, SMR=1.12, 95% CI=.95-1.31).

Table 4. Plants and Products Included in European Cohort Study (Boffetta et al., 1997)

Study Plant No.	Location	Principal FG Product	Beginning of Production	Latest Work History	No. of Workers
2	Finland	Glass wool	1941	1977	924
6	Norway	Glass wool	1935	1977	644
7	Sweden	Glass wool	1933	1977	2,022
10	U.K.	Glass wool	1943	1977	4,145
14	Italy	Glass wool	1946	1977	600
Total mostly wool					8,335
11	U.K.	Continuous filament	1946	1977	1,837
14	Italy	Continuous filament	1961	1977	1,722
Total filament only					3,559
All FG workers combined					11,894

[1] The NTP Draft Background Document notes on page 68, "[It should be noted that in the total cohort, the SMR for lung cancer was slightly higher among short-term workers with less than 1 year of employment (SMR=1.48, 95%CI=1.18-1.83, 83 deaths) than longer term workers...]". This is an inappropriate and potentially misleading comparison, as this SMR (taken from Table 2 of Boffetta et al., 1997) pertains to all workers including those exposed to rock/slag wool.

The largest plant (U.K, plant 10) included 109 or 78% of the observed lung cancer deaths among workers with at least one year of employment yielding a statistically significant 37% excess in deaths based on national reference rates (SMR=1.37, 95%CI=1.13-1.65). Workers from the U.K. plant with 30 or more years since first employment showed a not statistically significant 40% excess in lung cancer based on 29 deaths (SMR=1.40, 95%CI=.94-2.01). None of the other four plants studied revealed a statistically significant excess in lung cancer among workers with either one or more years of employment or 30 or more years since first employment.

SMR analyses of lung cancer (national reference rates) by technological phase (early, intermediate and late) for both all glass wool workers combined and those with at least one year of employment revealed no evidence of a trend suggestive of an association with glass fiber exposure. In fact, the SMR for both groups of glass wool workers was highest for workers first employed in the intermediate technologic phase. Likewise, lung cancer SMR analyses (national reference rates) revealed no evidence of an association with duration of employment or the time since first employment.

SMR analyses (national reference rates) for the other cancer site categories examined were essentially unremarkable, with the possible exception of a not statistically significant increased SMR for cancer of the oral cavity, pharynx and larynx based on 10 deaths (SMR=1.47, 95% CI=.71-2.71). Only one death due to mesothelioma was reported among the glass wool worker cohort (a subject from the U.K. plant).

Combined Cancer Incidence Study

Boffetta et al. (1999) reported a cancer incidence study of 2,611 glass wool workers with at least one year of employment in one of three European study plants located in countries with national cancer registries (Finland, Norway, Sweden). The cohort was followed for cancer incidence from plant start up date (range 1933-1941) until 1995. The authors reported an overall not statistically significant 28% excess in lung cancer cases (national reference rates) based on 40 cases (SIR=1.28, 95%CI=.91-1.74). A Poisson regression analysis of internal cohort rates revealed a not statistically significant increasing trend in lung cancer risk with increasing time since first employment [2], but no evidence of an association with increasing duration of employment (with a 15-year lag) or technological phase adjusted for gender, age, country and time since first employment. As in the combined mortality study, Boffetta et al. (1999) reported a not statistically significant increase in the SIR for cancers of the oral cavity, pharynx and larynx based on 16 cases (SIR=1.41, 95%CI=.80-2.28). No cases of mesothelioma were reported among workers in the glass wool study plants.

Nested Case-Control Study

Gardner et al. (1988) reported a nested, matched case-control study of lung cancers in the U.K. glass wool plant, which for some time also produced superfine fibers (1-3 μm diameter fibers made by flame attenuation and 2-5 μm diameter fibers made by rotary process). Information on manufacturing processes and job title or category were used to assign potential exposure to glass fiber and asbestos to cases and controls. Other than measurements taken in 1977 as part of

[2] On page 69 of the NTP Draft Background Document, the authors incorrectly refer to the analysis of lung cancer incidence by time since first employment as based on SIRs, when in fact, Boffetta et al. (1999) report (Table 4) relative risks (RRs) based on Poisson regression modeling of internal cohort incidence rates.

cohort study, no direct measures of glass fiber exposure were available. Additionally, no data on smoking or other co-exposures were available.

Based on 73 lung cancer deaths and 506 matched controls, the authors reported a not statistically significant 20% excess in risk for lung cancer for exposure to all respirable superfine and other glass wool fibers (RR=1.2, 95%CI=.70-2.00). Separately, lung cancer relative risks were 1.1 for glass wool (31 deaths, 95%CI=.70-1.90) and 1.3 for superfine fibers (2 deaths, 95%CI=.30-5.80). With the exception of an isolated statistically significant 2-fold excess in lung cancer risk for time since first employment among workers exposed to glass wool and/or superfine fibers (no CI given), the authors found no evidence of an association with increasing duration of employment or the time since first exposure or job category. Adjustment for potential asbestos exposure did not change the risk estimates for glass wool.

Background and Key Findings of Canadian Cohort Study

Shannon and coworkers (1984; 1987; 2005) studied a cohort of glass wool production workers in Ontario, Canada. The plant operated from 1948 until April 1991. Exposure measurements were available from 1977-1990 for ammonia, formaldehyde, phenol, carbon monoxide, solvents, asphalt fumes, total dust, crystalline silica and glass wool fibers. Glass fiber concentrations ranged from 0.01 to 0.32 fibers/ml with an average of 0.03 fibers/cc for that period, similar to that of the U.S. cohort (0.035 fibers/cc across all plants). Multipliers were used, based on production, automation and other factors, to adjust the 1977 to 1990 measurements to reflect historical exposures. Fibers, after adjustment, were still less than 1fiber/cc. The levels for other exposures, after adjustment, were less than current threshold limit values. Duration of exposure was used in place of quantitative exposure values, such as cumulative exposure. Date of first exposure was also examined because, anecdotally, fiber exposure levels were higher in earlier operating periods. The authors also examined risk by type of worker: plant only, office only and mixed.

The Canadian glass wool worker cohort included 2,557 men employed for at least 90 days between 1955 and 1997. In the 1987 update of glass wool workers, which followed workers through 1984, the authors identified 19 cases of lung cancer compared to 9.5 expected, a statistically significant elevation. In 2005, Shannon et al published the results of follow-up extended through 1997. In the 2005 update, they also added data on cancer incidence from the Canadian Cancer Registry, which was available from 1969 to 1996. The follow-up added approximately 30,000 person years of observation. Summarized below are the results of the latest 2005 follow-up, which are also considered in a later section as epidemiologic evidence published since the 2001 IARC decision to reclassify glass wool insulation as Group 3 (IARC, 2002).

In analyses by type of worker, plant-only workers revealed a statistically significantly increased SMR for lung cancer (42 deaths, SMR=1.63; 95%CI =1.18-2.21). The authors also found statistically significant elevations among workers employed 20 or more years and followed 40 or more years (7 deaths, SMR=2.82, 95%CI not given) and among all employees employed 20 or more years (17 deaths, SMR=1.89; 95%CI not given), however, SMRs did not vary consistently with duration of employment or the time since first employment. Lung cancer mortality was statistically significantly elevated in the pre-1960 hire group (31 deaths, SMR=1.72, 95%CI not

given) and not statistically significantly elevated in the 1960-1970 period (9 deaths, SMR=1.55, 95%CI not given).

The analysis of cancer incidence produced similar results. Lung cancer was the only statistically significantly elevated cancer among plant-only workers (50 cases, SIR=1.60, 95%CI=1.19-2.11). The authors also observed a slightly lower but still statistically significant elevation among all workers (54 cases, SIR=1.34, 95%CI=1.01-1.75).

The Canadian study of glass wool production workers found higher lung cancer SMRs than had been seen in other cohort studies of similar workers, however, the study found no consistent evidence of an association with duration of employment or the time since first employment. Shannon et al. (2005) conclude that "since exposure data are lacking from the early years of the plant, we cannot state if the excess was due to glass fibers, other work exposures or other reasons" (p. 528).

In an independent cohort study of Canadian glass filament workers, Shannon et al. (1990) found no evidence of increased mortality from lung associated with the manufacture of glass filaments.

Comparison of Features and Key Findings from the U.S., European and Canadian Cohort Studies

As noted above, the bulk of the epidemiological evidence regarding the long-term health effects of exposure to glass wool and/or glass filaments comes from the three historical cohort studies conducted in the U.S., Europe and Canada, and the U.S. study carries much of this evidence. Table 5 summarizes key features and comparable findings from each cohort study; Table 6 compares (in the first three columns) the methodological features of these studies. Methodological features are categorized as: (1) study population and follow-up, (2) exposure assessment, (3) case-control and other sub-studies and (4) statistical analysis.

Table 5 shows that the U.S, European and Canadian cohort studies are associated with similar cohort observation periods, glass fiber production start-up ranges, and exposure levels to respirable glass fibers. However, the U.S. cohort is by far the largest with more than three times as many subjects as the European cohort and more than 10 times as many subjects as the Canadian cohort. Table 6 shows that the U.S. cohort study is also by far the most methodologically comprehensive of the three cohort studies, having several important features not available in the European and Canadian study.

Among the most notable methodological features unique to the U.S. cohort study are: (1) quantitatively or qualitatively estimated historical exposures to respirable glass fibers and co-exposures known or suspected to be carcinogens; (2) a stratified probability sample of subjects to estimate the prevalence of smoking habits in the total cohort, and the use of this information to adjust study plant-specific lung cancer SMRs for confounding by smoking; (3) a nested case-control study of lung cancer that provided information on lifetime smoking histories used to adjust lung cancer odds ratios for confounding by smoking; (4) a detailed evaluation of mesothelioma mortality, including comparative mortality rate analysis and individual medical record and pathology specimen review for subjects whose death certificate mentioned "mesothelioma"; (5) a detailed exposure-response modeling of quantitative measures of respirable fiber exposure and lung cancer with adjustment for confounding by smoking and other

co-exposures and (6) exposure-response modeling for lung cancer using wide range of exposure-weighted measures of respirable fiber exposure (lagging, exposure time windows, etc.). Clearly, with its large size and many methodological features, the U.S. cohort study provides a substantial portion of the epidemiological data that NTP will rely upon as they consider delisting glass wool from the *12th Report on Carcinogens*.

Table 5 also shows that the U.S. and European investigators performed generally similar external and internal cohort mortality analyses that yielded remarkably similar results. While both studies found some isolated elevations for lung cancer, most of these were not statistically significant. Further, neither study found any consistent patterns in lung cancer mortality in relation to duration of employment or the time since first employment, or in relation to the roughly comparable factors, year of hire (U.S.) or technological phase (European). The U.S. study did not include lung cancer incidence, although this was not a serious limitation, as incidence and mortality findings in the European and Canadian studies were generally similar.

While the Canadian cohort study found statistically significantly elevated lung cancer SMRs in plant-only workers and in the highest duration of employment and time since first employment groups, there was, as in the U.S. and European studies, little consistent evidence of an association with duration or employment or the time since first employment. Notably, the lung cancer SMRs found in the Canadian study were considerably higher than those found in the much larger U.S. and European studies. Because the Canadian study did not include a nested case-control study or comparisons of internal cohort rates to enable control for potential confounding by smoking or other co-exposures, the Canadian investigators were unable to rule out some alternative explanations for their anomalous lung cancer findings.

Table 5. Key Features and Findings from the U.S., European and Canadian Cohort Studies of Glass Fiber Production Workers

Feature / Finding	U.S. Cohort Marsh et al. (2001a)	European Cohort Boffetta et al. (1997; 1999)	Canadian Cohort Shannon et al. (2005)
Subjects Mortality Cancer Incidence	 26,679 n/a	 8,335 2,611	 2,557 2,557
Plants studied Mortality Cancer Incidence	 8 n/a	 5 3	 1 1
Observation period (range) Mortality Cancer Incidence	 1946-92 n/a	 1933-90 (92) 1933-95	 1955-97 1969-96
Production start-up dates (range)	1940-64	1933-46	1948-91
Respirable glass fiber exposure level fibers/cm^3 (range)	0.034 - 0.350	0.01 – 1.00 [a.]	0.01 - 0.32 [b.]
Lung Cancer Mortality Findings	**Workers with > 1 yr employment (2 plants > 6 mos.)**	**Workers with > 1 yr employment**	**Plant-only workers > 90 days employment**
Number of deaths Glass wool Glass wool and filament	 243 490	 140 n/a	 42 n/a
Overall SMR (95% CI) local reference rates Glass wool Glass wool and filament	 1.18 (1.04-1.34) 1.02 (.94-1.12)	 1.12 (.95-1.31) n/a	 1.63 (1.18-2.21) n/a
SMRs (95%CI) by Duration of Employment (yrs) U.S. = all workers including glass filament Europe and Canada= glass wool workers	<5 1.10 (.99-1.22) 5-9 1.17 (.99-1.38) 10-19 0.88 (.74-1.04) 20-29 1.15 (.97-1.36) 30+ 0.97 (.76-1.22)	1-4 1.11 (.82-1.46) 5-9 1.18 (.80-1.68) 10-19 1.68 (1.23-2.25) 20+ 1.17 (.66-1.93)	1-4 1.50 (.80-2.56) 5-9 1.71 (.47-4.40) 10-19 1.39 (.60-2.75) 20+ 1.89 (1.10-3.03)
SMRs by Year of Hire (U.S and Canada) or Technological Phase (Europe) U.S. = all workers including glass filament Europe and Canada= glass wool workers	< 1950 1.01 (.92-1.11) 1950-59 1.17 (1.05-1.30) 1960-69 0.95 (.75-1.18) 1970-77 1.09 (.69-1.63)	Early 1.07 (.64-1.67) Interm. 1.40 (1.14-1.70) Late 1.02 (.63-1.56)	< 1960 1.72 (1.17-2.44) 1960-70 1.55 (.71-2.95) 1970+ 1.01 (.12-3.65)

Feature / Finding	U.S. Cohort Marsh et al. (2001a)	European Cohort Boffetta et al. (1997; 1999)	Canadian Cohort Shannon et al. (2005)
SMRs by Time Since First Employment (yrs) U.S. = all workers including glass filament Europe and Canada= glass wool workers	<20 0.92 (.77-1.10) 20-29 0.99 (.87-1.14) 30-39 1.14 (1.02-1.27) 40+ 1.15 (1.00-1.32)	> 30 1.43 (1.04-1.91)	<10 2.41 (.29-8.70) 10-19 1.39 (.45-3.24) 20-29 1.83 (1.02-3.01) 30-39 1.20 (.60-2.15) 40+ 2.28 (1.04-4.34)
Lung Cancer Incidence Findings	**n/a**	**Workers with > 1 yr employment**	**> 90 days employment**
Number of cases (glass wool workers)	--	40	50 (plant only) 54 (all workers)
Overall SIR (95%CI) (glass wool workers)	--	1.28 (.91-1.74)	1.60 (1.19-2.11) (plant only) 1.34 (1.01-1.75) (all workers)
Lung Cancer Internal Cohort Rate Comparisons	**Matched case-control study of deaths, 1970-92 (all males with 1+ yrs employment[c], 632 deaths, 572 controls, adjusted for smoking)**	**Poisson regression analysis of incidence rates, (workers with 1+ yrs employment, unadjusted for smoking)**	**n/a**
RRs (95%CI) by Duration of Employment (yrs) U.S. = all workers including glass filament Europe = glass wool workers	<5 1.00 baseline 5-9 1.16 (.76-1.76) 10-19 0.84 (.58-1.21) 20-29 1.02 (.72-1.45) 30+ 0.77 (.52-1.16) Global test p-value=0.49	1-4 1.00 baseline 5-9 0.80 (.30-2.00) 10-19 0.80 (.30-2.40) 20+ 0.70 (.08-5.30) Trend test p-value=0.50	--
RRs (95%CI) by Time Since First Employment (yrs) U.S. = all workers including glass filament Europe = glass wool workers	<20 1.00 baseline 20-29 0.79 (.46-1.34) 30-39 0.84 (.49-1.45) 40+ 0.97 (.52-1.79) Global test p-value=0.66	1-9 1.00 baseline 10-29 1.90 (.80-4.80) 30+ 2.30 (.60-9.20) Trend test p-value=0.20	--

a. Based on contemporary exposure measurements for four plants (Cherrie et al., 1986)
b. Based on limited exposure measurements made by the company during 1977-90
c. Six months for Plant Nos. 1 and 6

Table 6. Methodological Features of the U.S., European and Canadian Cohort Studies and Relevant Post-2001 Studies of Glass Fiber Production Workers

Methodological Feature	Combined Cohort Studies			Post-2001 Studies		
	U.S. [a.]	Europe [b.]	Canada [c.]	Pintos et al. (2008)	Baccarelli et al. (2006)	Carel et al. (2007)
Study Population and Follow-up						
Cohort enumeration verified to be complete via formal process	●	○	●	n/a	n/a	n/a
Inclusion of male and female subjects	●	●	○	●	●	○
Availability of information of race/ethnicity of individual subjects	●	○	○	○	○	○
Inclusion of substantial portion of subjects employed 10+ years and followed 20+ years	●	●	●	n/a	n/a	n/a
Vital status found for >95% of cohort	●	●	●	n/a	n/a	n/a
Cause of death found for >95% of known deaths	●	●	●	n/a	n/a	n/a
Exposure Assessment						
Availability of detailed work histories for all individual members of the cohort	●	●	●	●	●	●
Quantitatively estimated historical exposures to respirable glass fibers	●	○	○	○	○	○
Qualitatively estimated historical exposures to respirable glass fibers	●	●	○	●	●	●
Quantitatively estimated historical exposures to co-exposures known or suspected to be carcinogens	●	○	○	○	○	○
Qualitatively estimated historical exposures to co-exposures known or suspected to be carcinogens	●	○	○	●	●	●

Methodological Feature	Combined Cohort Studies			Post-2001 Studies		
	U.S. [a.]	Europe [b.]	Canada [c.]	Pintos et al. (2008)	Baccarelli et al. (2006)	Carel et al. (2007)
Case-Control and other Sub-Studies						
Nested case-control study of lung cancer to enable control for confounding by smoking and other co-exposures in assessment of exposure-response for respirable fibers and lung cancer	●	●	○	n/a	n/a	n/a
Stratified probability sample of subjects to estimate prevalence of smoking habits in total cohort	●	○	○	n/a	n/a	n/a
Use data from smoking survey to indirectly adjust study plant-specific lung cancer SMRs for confounding by smoking	●	○	○	n/a	n/a	n/a
Use data from nested case-control study to adjust odd ratios lung cancer for confounding by smoking	●	○	○	●	○	●
Detailed evaluation of mesothelioma mortality, including comparative mortality rate analysis and individual medical record and pathology specimen review for subjects whose death certificate mentioned "mesothelioma"	●	○	○	○	○	○
Lung cancer incidence study with cases identified by tracing cohort through national, regional or hospital tumor registries	○	●	●	●	○	●
Statistical Analysis						
80% or greater statistical power to detect 1.5-fold or greater excess in lung cancer among subjects exposed to glass fibers	●	●	○	○	○	○
External mortality comparisons via SMRs based on national and local rates	●	●	○	n/a	n/a	n/a
Internal mortality comparisons via relative risk regression modeling or Poisson regression analysis of internal cohort rates	●	●	○	n/a	n/a	n/a
Detailed exposure-response modeling of quantitative measures of respirable fiber exposure and lung cancer with adjustment for confounding by smoking and other co-exposures	●	○	○	○	○	○

Methodological Feature	Combined Cohort Studies			Post-2001 Studies		
	U.S. [a.]	Europe [b.]	Canada [c.]	Pintos et al. (2008)	Baccarelli et al. (2006)	Carel et al. (2007)
Exposure-response modeling of qualitative measures of respirable fiber exposure and lung cancer with adjustment for confounding by smoking and other co-exposures	●	●	○	●	●	●
Exposure-response modeling for lung cancer using wide range of exposure-weighted measures of respirable fiber exposure (lagging, exposure time windows, etc.)	●	○	○	○	○	○

a. Buchanich et al., 2001; Marsh et al., 2001a, 2001b, 2001c; Quinn et al., 2001; Smith et al., 2001; Stone et al., 2001; Youk et al., 2001
b. Boffetta, et al., 1997; 1999
c. Shannon et al., 1984; 1987; 2005
● Feature present
○ Feature absent
n/a Feature not applicable to this study

Evaluation of Epidemiology Evidence Available Since the 2001 IARC Review

The primary aim of this evaluation was to determine whether the collective epidemiological and other relevant research published since the 2001 IARC review of glass fibers alters in any way IARC's decision to downgrade glass insulation wool from Group 2B to Group 3 (IARC, 2002), thus possibly impacting NTP's pending decision to delist glass wool (respirable size) from the upcoming *12th Report on Carcinogens*. My review and evaluation (with the assistance of my colleagues Drs. Ada Youk and Jeanine Buchanich) of post-IARC studies of workers with glass wool or other MMVF exposure, included a meta-analysis (Berrigan, 2002), a study estimating exposures for insulation installers (Maxim et al., 2003), a cohort study of gastrointestinal cancer among Finnish women (Weiderpass, 2003), a case-report of pulmonary fibrosis (Guber et al., 2006), three case-control studies (Baccarelli et al., 2006; Carel et al., 2007; Pintos et al., 2008) and further evaluations of the U.S. (Stone et al., 2004) and Canadian (Shannon et al., 2005) cohorts.

This section includes a detailed review of each post-2001 study, a summary of the key findings of these studies as they weigh on the specific aim of this evaluation and a comparison of the methodological features of the relevant post-2001 studies. Based on the results of this evaluation, I conclude that IARC's 2001 decision that "glass wool insulation" was not classifiable as to its carcinogenicity in humans remains valid in light of the relatively uninformative additional epidemiological evidence provided by the post-2001 studies, thereby supporting NTP's consideration of delisting glass wool insulation.

Detailed Reviews

Berrigan (2002)

Berrigan reports the results of a meta-analysis of 10 published cohort studies and 10 published case-control studies that analyzed the relationship between MMVF exposure and respiratory system cancer. Medline was used to identify the studies as well as a manual review of the references from the identified papers. The ten cohort studies that were included were: Enterline and Henderson (1975), Morgan et al.(1981), Shannon et al. (1987), Shannon et al. (1990), Gustavsson et al. (1992), Marsh et al. (1996), Chiazze et al. (1997a,b), Watkins et al. (1997), Bofetta et al. (1997) and Marsh et al. (2001a). The cohorts ranged in size from the smallest of 416 subjects (2262 person-years) to over 32,000 subjects (almost 1,000,000 person-years). Respiratory system cancer SMRs for MMVF exposures ranged from 0.50 to 1.99 and all but three of the estimated SMRs were over one.

The meta-analysis resulted in a statistically significant combined SMR of 1.23 (95% CI=1.13-1.33) for exposure to MMVF. Combined respiratory system cancer SMRs by MMVF exposure type were also elevated and statistically significant for glass wool and rock wool (glass wool SMR=1.23, 95% CI=1.10-1.38; glass filament SMR=1.08, 95% CI=0.93-1.26; rock wool SMR=1.32, 95% CI=1.15-1.52). National rates were used for in the computation of the overall MMVF SMR for all studies. For the SMR by MMVF type, only Marsh et al. (2001a) used local rates which reduced the estimated risks slightly.

The 10 case-control studies were: Kjuus et al. (1986a,b), Enterline et al. (1987), Engholm et al. (1987), Gardner et al. (1988), Wong et al. (1991), Chiazze et al. (1992, 1993), Marsh et al.

(1996), Chiazze et al. (1993,1995), Bruske-Hohlfeld et al. (2000) and Marsh et al. (2001a). Combined estimates were not computed over the ten case-control studies, the individual relative risk (RR) estimates were heterogeneous and several studies only reported risk estimates by level of MMVF exposure. Odds ratios ranged from 0.59-1.43. Nine of the 10 studies were nested in cohort studies of MMVF production workers. Eight of the ten studies adjusted for smoking. In most cases, the estimated RSC risks were lower after adjustment for smoking.

As acknowledged by the author, because this meta-analysis did not evaluate the available epidemiological evidence on the exposure-response relationship between glass fibers and lung cancer (e.g., Marsh et al. 2001a, Youk et al., 2001, Stone et al., 2001) the results should be considered as incomplete.

Maxim et al. (2003)

Glass wool insulation is used in residential, commercial and industrial buildings and is installed by professional installers in all three building types and as do-it-yourself (DIY) projects in residences. Installation does not have the same comprehensive exposure assessment data available from the manufacture of glass wool insulation, yet there are more persons exposed to glass wool insulation during installation than during manufacturing. For these reasons, Maxim et al. (2003) conducted a study of the exposure potential of professional and DIY installers and compared those to the exposures experienced by workers producing glass wool insulation.

The authors calculated potential exposure levels for DIY and professional installers. The exposure time for DIY installers was calculated as: 8.4 projects per lifetime (the average number of moves each person makes) x 9hr/project x 1day/8hr x 1 year/240 working days x 12 months/year = 0.47 months/lifetime of exposure. The level of glass wool fiber exposure was taken from the Marchant et al. (2002) study of installation of glass wool batts and blankets. The mean fiber/cc concentration for installers was 0.17 f/cc. The total cumulative exposure for DIY installers is 0.47 months x 0.17 f/cc = 0.08 f-months/cc.

The range of median cumulative exposure to respirable fibers was 1.839 to 6.382 f-months/cc in the U.S. cohort study of MMVF workers in the mainly glass wool plants (Plants 1, 4, 6, 11 and 14). The range of mean cumulative exposures in these plants was 5.032 to 13.408 f-months/cc. The cumulative exposure levels estimated for DIY installers in the Maxim et al. article are 50 to 100 times below those experienced by glass wool production workers.

The exposure time for professional installers was calculated by estimating the tenure in installation jobs or jobs with potential glass wool exposure. The estimated median tenure from the US Department of Labor, Bureau of Labor Statistics was 8 years. The authors also estimated that, for professional installers, 4.3 hrs of each 8 hr work day had glass wool exposure over the 51.60 months in the standard career. They then weighted the estimates for type of glass wool installed (batt/blanket, blown with binder, blown without binder) and for estimated respirator use. The range of cumulative exposure to glass wool among professional installers was estimated to be 4.22 f-months/cc to 7.28 f-months/cc.

Maxim et al. used, as their benchmark, mean cumulative respirable fiber level from the plant with the highest cumulative level in the U.S. cohort (Plant 10) (Marsh et al., 2001a) and concluded that professional installers experienced glass wool exposures 3 to 5 times below those

experienced in the U.S. cohort. The mean cumulative level for all fiberglass plants was 6.080 f-cc/months in the Marsh et al. study. If the mean cumulative level for all fiberglass plants is used, the range of cumulative fiber exposure for professional installers is similar to that of the U.S. cohort.

The authors state that their key finding is that the average cumulative exposures of both DIY and professional installers are substantially lower than the benchmark values (Plant 10 mean cumulative respirable fiber level) and that estimated cumulative exposures are lower for installers than for manufacturers. They conclude that these results are reassuring in light of the negative results in the U.S. studies.

Weiderpass et al. (2003)

Weiderpass et al. describe the results of a large Finnish cohort of women who were occupationally exposed to 31 agents. Women included in the cohort were born in Finland during the time period 1906-1945 (n=413,877). The cohort was traced for incident cases of cancer of the gastrointestinal tract during 1971-1995. Detailed work history records were available through census records and were linked to a national job-exposure matrix. Internal comparisons of low to high exposures were made using Poisson regression. Models were fit to estimate relative risks (RRs) for exposure, standardized for birth cohort, follow-up period and socioeconomic status. While not statistically significant, Weiderpass et al., noted an increasing trend in esophageal cancer with increasing levels of MMVF exposure (no exposure, RR=1.00; low exposure, RR=1.29, 95% CI=0.83-2.00; medium/high exposure, RR=1.61, 95% CI=0.80-3.25). There was also a statistically significant 23% excess of stomach cancer risk in the MMVF low exposed group (RR=1.23, 95% CI=1.01-1.49) and a not statistically significant 23% and 34% excesses for the medium/high exposed group for stomach and pancreatic cancer, respectively (stomach-RR=1.23, 95% CI=0.85-1.77; pancreatic-RR=1.34, 95% CI=0.89-2.03). The authors conclude that the results of this study are suggestive of a positive relationship between MMVF exposure and gastrointestinal cancers.

Because this report focuses on gastrointestinal cancers, Weiderpass et al. (2003) is not relevant in assessing the relationship of MMVF exposure with RSC. Not statistically significant excesses of stomach, intestine and rectum cancers have been noted previously in other studies of MMVF exposure (Boffetta et al. 1997, Gardner et al., 1986, Andersen and Langmark, 1986, Morgan et al. 1981).

Stone et al. (2004) (Subset of U.S. cohort study)

Stone et al. report the 1946-1992 mortality experience of 4008 female production workers from the U.S. cohort study. The plants were grouped according to MMVF type: filament plants (2, 5), wool and filament plants (9, 10, 15) and mostly wool plants (1, 4, 6, 11, 14). Female workers represented 12.5% of the total U.S. cohort and contributed 9.5% of the total person-years of active employment (person-years of active employment = 30,237). Almost 90% of the person-years were associated with respirable fiber exposure. Among those females exposed to respirable fibers, the levels of exposures were low. The median estimated average respirable fiber exposures were 0.001 fibers/cc in the filament plants, 0.008 fibers/cc in the wool and filament plants and 0.059 fibers/cc in the mostly wool plants. These averages were lower than the corresponding values estimated for the males.

There were no statistically elevated SMRs (based on national and local comparisons) observed for all cause mortality or any of the nonmalignant causes of death considered. The local based SMR for nonmalignant respiratory disease excluding influenza and pneumonia (NMRDxIP) was 1.02 (95% CI=0.74-1.37). For most of the malignant causes considered, the SMRs were less than one (based on national and local comparisons). The respiratory system cancer (RSC) SMR was 1.01 (95% CI=0.76-1.32) based on local comparisons. Other not statistically significant elevated SMRs were seen for cancer of the cervix (national based SMR=1.02, 95% CI=0.52-1.78) and for cancer of the bladder and other urinary organs (national based SMR=1.93, 95% CI=0.83-3.80; local based SMR=1.62, 95% CI=0.70-3.20). Analyses were also shown for RSC and NMRDxIP based on long term workers (5+ years of employment). The SMR was 1.20 (95% CI=0.78-1.76) for RSC and 1.06 (95% CI=0.64-1.66) for NMRDxIP.

Internal comparisons were also made for RSC. There was no statistically significant heterogeneity seen across the 10 plants, however heterogeneity was apparent among the type of MMVF. RSC mortality was elevated in the mostly wool plants relative to the filament plants (RR=3.24, 95% CI=1.27-8.28, based on 4 deaths) and not statistically significantly elevated in the wool and filament plants compared to the filament plants (RR=1.36, 95% CI=0.76-2.45). Overall exposure to respirable fibers showed no evidence of RSC mortality risk (RR=1.0, 95% CI=0.96-1.06). There was an increased risk in RSC mortality for those women not exposed to respirable fiber or those women exposed to both respirable fiber and formaldehyde as compared to those with exposure to respirable fiber but no formaldehyde. No patterns emerged in RSC risk by increasing levels of duration of employment or time since first employment. In multivariable models, the estimated RSC RRs associated with a one fiber/cc increase in cumulative respirable fiber exposure ranged from 0.98-1.00. All of the multivariable models adjusted MMVF type and formaldehyde exposure, with additional adjustments for year of hire, duration of employment or time since first employment.

The authors concluded that both external and internal mortality comparisons show no evidence of increased RSC risk related to respirable fiber exposure at the levels estimated for these workers.

Shannon et al. (2005) (Update of Canadian Cohort Study)

This most recent update of the Canadian cohort study reported earlier by Shannon et al. (1984; 1987) was described and discussed in detail in an earlier section of the comments. In summary, the additional evidence provided by the post-2001 update of the Canadian cohort study was essentially similar to that available from this study at the time of the IARC 2001 review.

Baccarelli et al. (2006)

Baccarelli et al. conducted a case-control study to investigate the association of lung cancer risk with exposure to dusts and fibers (DF) in the Leningrad Province of Russia. 540 cases (474 male, 66 female) of lung cancer were identified via autopsies performed by the St. Petersburg Central Pathology Laboratory for the Leningrad Province from 1993-1998. 582 cases (453 male, 129 females) were also selected from deceased subjects who were not identified as having lung cancer. Controls who died from smoking related diseases were excluded. Controls were frequency matched to the cases by gender, age, region and year of death. Health related

information, including smoking, was obtained for both cases and controls from local health services and hygiene centers.

Detailed job histories for each subject were reviewed to identify the relevant exposure data collected by the local hygiene centers. Exposure data were extracted by 17 occupational physicians with expertise in historical workplace exposures. Each exposure was classified as to the presence, intensity, frequency and duration. Maximum allowable concentrations (MACs) were used to standardize the calculation of the exposure intensities for the respirable fibers. Gender-specific multivariate logistic regression models were fit to estimate the odds ratio (OR) for lung cancer risk associated with dust and fiber exposure. These models were adjusted for age, smoking, region of residence and in some cases asbestos exposure.

Male subjects exposed to man-made vitreous fibers (MMVF) showed a not statistically significant excess in lung cancer risk based on 23 cases and 15 controls (OR=1.82, 95% CI=0.88-3.75). Ten lung cancer cases (and five controls) were exposed only to glass wool resulting in a not statistically significant 77% excess (OR=1.77, 95% CI=0.57-5.51). An over 3-fold statistically significant excess was seen for other MMVFs (excluding glass wool but including slag wool and ceramic fibers) based on 14 cases and seven controls (OR=3.34, 95% CI=1.18-9.45). Additional adjustment for asbestos exposure (identified among four lung cancer deaths) resulted in reduced, not statistically significant ORs for MMVF exposure (OR=1.72, 95%CI=.83-3.89) and glass wool exposure (OR= 1.56, 95%CI=.49-5.02) and a reduced but statistically significant OR for other MMVF exposure (OR=3.25, 95%CI=1.16-9.11). Analysis of lung cancer risk in relation to MMVF, glass wool and other MMVF exposure by duration of exposure (<10, 10+ yrs), average intensity of exposure (<75%MAC, 75%MAC+) and cumulative exposure score (as product of average intensity score and duration (<5, 5+)) revealed no consistent evidence of any exposure-response relationships.

This study was limited by the small number of cases and controls who had exposure to MMVF, glass wool or other MMVFs. In addition, the possibility of chance findings to the large number of comparisons could not be excluded. The authors conclude that their study showed increased lung cancer risks for selected categories of dusts and fibers, but the evidence for workers exposed to glass wool only was essentially unremarkable in light of the study's limitations.

Guber et al. (2006)

Guber et al. describe, in a case report, the clinical care of a 41 year old man with an initial complaint of shortness of breath. He worked as a bus driver on the same vehicle from 1984 to 1995; the roof of the bus was insulated with glass wool and the covering was full of holes. Sputum examination and lung biopsy revealed fibers shorter than 20 μm, resembling the morphology and chemical composition of those found in glass wool insulation. The authors indicate that the histological findings and lung CT scans resemble pulmonary fibrosis. They conclude that this case represents "a case of interstitial lung disease probably caused by low fibrogenic activity glass wool fibers" (page 1,069). As a case-report with no study or comparison populations, this study is not informative regarding the potential health effects of glass fiber exposure.

Carel et al.(2007)

The lung cancer mortality rates in Central and Eastern European countries are some of the highest in the world and high levels of asbestos are still found in these countries. Because asbestos was replaced in many operations by man-made vitreous fibers (MMVF), concern about the carcinogenic role of these fibers also exists. Carel et al. (2007) conducted a very large, multicenter, population-based case-control study to investigate the relationship between occupational exposure to asbestos and man-made vitreous fibers and lung cancer. The study, conducted from 1998-2002, included all incident lung cancer cases (age <75 years) diagnosed in 16 participating centers in seven European countries. Controls were recruited from the same hospitals as the lung cancer cases in most cases; controls from Warsaw and Liverpool were recruited from population-based listings. The response rate was 84% among cases and 85% among controls for a total of 2205 male lung cancer cases and 2305 controls frequency matched on age (± 3 years) and sex in the study.

Detailed work histories were obtained during face-to-face interviews; 18 occupations had special, detailed questionnaires. Exposure to 70 agents was assessed; "asbestos" and "MMVF" variables were created which encompassed exposure to any fiber type of these two exposure groups. Exposures were categorized as possible, probable or certain; frequency and intensity of exposure were also evaluated. MMVF cutpoints were <0.1 fibers/ml for low, 0.1-1 fibers/ml for medium and >1 fibers/ml for high exposure.

5.2% of the cases and 3.9% of controls were ever exposed to MMVF. The odds ratio for lung cancer among men ever exposed to MMVF was 1.23 (95%CI .088-1.71). There were some elevations by exposure intensity, duration of exposure and cumulative exposure but no significant trends (p=0.87, 0.10 and 0.62, respectively). There was no significant modification in effects with analyses stratified by smoking or occupational exposure to asbestos.

This study found no relationship between MMVF exposure and lung cancer in this very large, population based case-control study. The authors collected extensive information on work history, smoking and lifestyle factors in face-to-face interviews. Because interviews were used, recall bias could be a concern. However, questions were in terms of occupation rather than exposure and exposures to 70 agents were evaluated, which should make the effect of response bias on MMVF results negligible. Exposure assessment was on a qualitative rather than quantitative basis. Power in the study was low due to the small number of exposed subjects and because most MMVF exposed subjects were exposed to low levels.

The authors concluded that, in their community-based study of occupational exposure, MMVF exposure does not appear related to the high lung cancer burden experienced by Central and Eastern European men.

Pintos et al (2008)

Pintos et al. summarizes the results of two population-based case-control studies in Montreal Canada that were conducted to examine the effects of occupational asbestos and man-made vitreous fibers (MMVF) on the risk of being diagnosed with lung cancer. Study I was conducted from 1979-1986 and included incident (histologically confirmed) cases of cancer identified in all of the major hospitals in Montreal Canada. The cases were male and aged 35-70 at diagnosis.

Population based controls were selected from electoral lists and frequency matched to each case based on age and area of residence. A second set of controls was also considered which included 1,349 cancer patients (not diagnosed as a lung cancer) who were diagnosed in the same year and hospital as the lung cancer cases. Study II was conducted from 1996-2001 and included incident (histologically confirmed) cases of lung cancer identified in all of the major hospitals in Montreal Canada. The cases were male and aged 35-75 at diagnosis. Population based controls were individually matched based on the age, sex and area of residence of the lung cancer cases.

For both studies the interview included a section that collected sociodemographic and lifestyle information, including ethnicity, family income and smoking history and a section that collected detailed work history across the subjects working lifetime. For each job held, questions were asked about the company, products produced, worksite environment, job tasks and any other information that could provide insight about work exposures and associated intensity. A team of chemists and industrial hygienists reviewed each completed questionnaire and assigned each job a potential exposure from a list of 294 agents. For each agent considered, three types of information were detailed: the degree of confidence that the exposure actually occurred (possible, probable, definite), the frequency of exposure in a normal work week (<5%, 5-30%, >30%) and the relative level of exposure (low, medium, high). Non-exposure was considered as exposure up to the level found in the general environment.

In Study I, there were 1082 lung cancers and 740 population controls. Of these, 857 (79%) of the cases and 533 (72%) of the controls were interviewed. Study II identified 858 lung cancer cases and 1024 matched controls. Eighty-six percent of the cases and 70% of the controls completed the interview. Lifetime prevalence of occupational exposure to MMVF for the lung cancers cases was similar to the controls across all levels of exposure (non-exposed, non-substantial, substantial) for both studies with the lowest prevalence being at the substantially exposed level. The most common occupations for workers exposed to MMVF were from the construction industry.

In both studies, multivariate logistic regression models were fit to estimate the odds ratio (OR) for lung cancer risk associated with MMVF exposure. These models were adjusted for age, family income, education, ethnicity, respondent status (self, proxy) and tobacco smoking. For Study I, a combined set of controls were used because adjusted ORs were similar when using the population-based controls or the cancer controls. Using this combined set of controls, there was no increased risk of lung cancer associated with exposure to MMVF (OR=0.94, 95% CI=0.64-1.38). Study II showed a 20% excess lung cancer risk for overall exposure to MMVF (OR=1.20, 95% CI=0.78-1.83). Exposure to a substantial level of MMVF resulted in a 48% excess of lung cancer risk (OR=1.48, 95% CI=0.52-4.21). The pooled results of both studies showed a small excess of lung cancer risk for MMVF exposure (OR=1.05., 95% CI=0.80-1.40).

Because some subjects were exposed to both asbestos and MMVF, analyses were performed on subjects who only had MMVF exposure. Results from the pooled analysis showed excess risks at the substantial (OR=1.10, 95% CI=0.37-3.22) and non-substantial (OR=1.59, 95% CI=0.94-2.67) levels of MMVF exposure. These risks were not statistically significant. It appears that no exposure response relationship exists, however, the numbers exposed at the substantial level were small (8 cases, 9 controls). Strengths of these studies include the collection of lifetime history of smoking and detailed job histories. These studies were limited by the low statistical power due to small numbers of exposed individuals and by the lack of quantitative exposure

data. The authors conclude that the results of the analysis for MMVF exposure are compatible with no excess risk of RSC, however they caution that a positive association between MMVF exposure and RSC risk cannot be ruled out.

Summary of Findings for Post-2001 Studies

The relevant epidemiological or other studies available since the 2001 IARC decision that "glass wool insulation" was not classifiable as to its carcinogenicity in humans (IARC, 2002) consist of a meta-analysis (Berrigan, 2002), a cohort study of gastrointestinal cancer among Finnish women (Weiderpass, 2003) a case-report of pulmonary fibrosis (Guber et al., 2006), a study estimating exposures for insulation installers (Maxim et al., 2003), three case-control studies (Pintos et al., 2008; Carel et al., 2007; Baccarelli et al., 2006) and further evaluations of the U.S. (Stone et al., 2004) and Canadian (Shannon et al., 2005) cohorts.

Only the three case-control studies (Pintos et al., 2008; Carel et al., 2007; Baccarelli et al., 2006) provided new epidemiological evidence independent of the U.S., European and Canadian cohort studies, which provided the bulk of the evidence at the time of the IARC 2001 decision. Table 6 compares the methodological features of the three relevant post-2001 studies of glass fiber production workers with those of the U.S., European and Canadian cohort studies. Table 6 shows that relative to the U.S. and European cohort studies, and in some cases, the Canadian cohort study, the three post-2001 case-control studies were relatively uninformative regarding the potential carcinogenicity of glass wool fibers.

None of the three post-2001 case-control studies revealed consistent evidence of a increased lung cancer risk in relation to glass fiber exposure. While the Baccarelli et al. (2006) autopsy-based case-control study showed increased lung cancer risks for selected categories of dusts and fibers, the evidence for workers exposed only to glass fibers was essentially unremarkable in light of the study's limitations.

Stone et al. (2004) performed a detailed evaluation of female workers from the U.S. cohort and Shannon et al. (2005) extended follow-up of the Canadian cohort and included a new cancer incidence study. In effect, the results of both post-2001 reevaluations did not change the overall conclusions reached from the earlier evaluations considered by IARC in 2001.

A key finding of the Maxim et al. exposure assessment was that the average cumulative exposures of both professional and do-it-yourself (DIY) installers are substantially lower than the benchmark values (U.S. cohort study, Plant 10 mean cumulative respirable fiber level) and that estimated cumulative exposures are lower for installers than for manufacturers. As noted by the authors, these results are reassuring in light of the lack of evidence of an exposure-response for lung cancer in the U.S. cohort study.

Conclusion

My evaluation of the collective epidemiological and other scientific evidence published since the 2001 IARC review revealed that IARC's 2001 decision to downgrade glass insulation wool from Group 2B to Group 3 remains valid and, as such, NTP should weigh the IARC 2001 decision heavily as they consider delisting glass wool (respirable size) from the upcoming *12th Report on Carcinogens*.

References Cited

Andersen A, Langmark F. Incidence of Cancer in the Mineral-Wool Producing Industry in Norway. *Scand J Work Environ Health* 1986; 12(suppl 1): 72-77.

Axelson O, Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. *Am J Ind Med* 1988; 13:105-118.

Baccarelli A, Khmelnitskii O, Tretiakova M, Gorbanev S, Lomtev A, Klimkina I, Tchibissov V, Averkina O, Rice C, Dosemeci M. Risk of Lung Cancer from Exposure to Dusts and Fibers in Leningrad Province, Russia. *Am J Ind Med* 2006; 49:460-467.

Berrigan D. Respiratory Cancer and Exposure to Man-Made Vitreous Fibers: A Systematic Review. *Am J Ind Med* 2002; 42:354-362.

Boffetta P, Saracci R, Andersen A, Bertazzi P, Chang-Claude J, Ferro G, et al. Lung cancer mortality among workers in the European production of man-made mineral fibers- a Poisson regression analysis. *Scand J Work Environ Hlth* 1992; 18:279-286.

Boffetta P, Saracci R, Andersen A, Bertazzi PA, Chang-Claude J, Cherrie J, Ferro G, Frentzel-Beyme R, Hansen J, Olsen J, Plato N, Teppo L, Westerholm P, Winter PD, Zocchetti C. Cancer Mortality among Man-Made Vitreous Fiber Production Workers. *Epidemiology* 1997; 8(3):259-268.

Boffetta P, Andersen A, Hansen J, Olsen J, Plato N, Teppo L et al. Cancer Incidence among European man-made vitreous fiber production workers. *Scand J Work Environ Hlth* 1999; 25(3) 222-226.

Bruske-Hohlfeld I, Mohner D, Pohlabein H, Ahrens W, Bolm-Audorff U, Kreienbrock L, Kreuzer M, Jahn I,Wichman H-E, Jockel K-H. Occupational lung cancer risk for men in Germany: Results from a pooled case-control study. *Am J Epidemiol* 2000; 151:384–395.

Buchanich JM, Marsh GM, Youk AO. Historical cohort study of U.S. fiber glass production workers: V. Tobacco smoking habits. *J Occup Environ Med* 2001; 43:793-802.

Carel R, Olsson AC, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabianova E, Cassidy A, Mates D, Bencko V, Foretova L, Janout V, Fevotte J, Fletcher T, 't Mannetje A, Brennan P, Boffetta P. Occupational exposure to asbestos and man-made vitreous fibres and risk of lung cancer: A multicentre case-control study in Europe. *Occup Environ Med* 2007; 64:502-508.

Cherrie J, Dodgson J, Groat S, Maclaren W. Environmental surveys in the European man-made mineral fiber production industry. *Scand J Work Environ Health* 1986; 12(Suppl 1):18-25.

Chiazze L, Watkins D, Fryar C, Kozono J. A case-control study of malignant and non-malignant respiratory disease among employees of a fibreglass manufacturing facility. *Brit J Ind Med* 1992; 49:326-333.

Chiazze L, Watkins D, Fryar C, Kozono J. A case-control study of malignant and non-malignant respiratory disease among employees of a fibreglass manufacturing facility. II. Exposure assessment. *Brit J Ind Med* 1993; 50:717-725.

Chiazze L, Watkins D, Fryar C. Adjustment for the confounding effect of cigarette smoking in an historical cohort study of workers in a fiberglass manufacturing facility. *J Occup Environ Med* 1995; 37: 744-748.

Chiazze L, Watkins D, Fryar C. Historical cohort mortality study of a continuous filament fiberglass manufacturing plant. I. White men. *J Occup Environ Med* 1997a; 39:432-441.

Chiazze L, Watkins D, Fryar C. Historical cohort mortality study of a continuous filament fiberglass manufacturing plant. II. Women and minorities. *J Occup Environ Med* 1997b; 39: 548-55.

Chiazze L, Watkins D, Fryar C, Fayerweather W, Bender J, Chiazze M. Mortality from nephritis and nephrosis in the fibreglass manufacturing industry. *Occup Environ Med* 1999; 56:164-166.

Consonni D, Boffetta P, Andersen A, Chang-Claude J, Cherrie J, Ferro G. Lung cancer mortality among European rock/slag wool workers: exposure-response analysis. *Cancer Cause and Control* 1998; 9:411-416.

Doll, R. Symposium on MMMF, Copenhagen, October 1986: Overview and conclusions. *Annals of Occupational Hygiene* 1987; 31:805-819.

Engholm G, Englund A, Fletcher AC, Hallin N. Respiratory cancer incidence in Swedish construction workers exposed to manmade mineral fibres and asbestos. *Ann Occup Hyg* 1987; 31:663–675.

Enterline PE, Henderson V. The health of retired fibrous glass workers. *Arch Environ Health* 1975; 30:113-116.

Enterline PE, Marsh GM, Esmen NA. Respiratory disease among workers exposed to man-made mineral fibers. *Am Rev Respir Dis* 1983; 128:1-7.

Enterline PE, Marsh GM. The health of workers in the MMMF industry. In: Biological Effects of Man-Made Mineral Fibres. Copenhagen:World Health Organization, Regional Office for Europe:1984; 1:311-339.

Enterline PE, Marsh GM, Henderson V, Callahan C. Mortality update of a cohort of US man-made mineral fiber workers. *Ann Occup Hyg.* 1987; 31:625-656.

Esmen N, Hammad Y, Corn M, Whittier D, Kotsko N, Haller M, Kahn, R. Exposure of employees to man-made mineral fibers: Mineral wool production. Environ Res 1978; 15(2):262-277.

Esmen N, Corn M, Hammad Y, Whittier D, Kotsko N. Summary of measurements of employee exposure to airborne dust and fiber in sixteen facilities producing man-made mineral fibers. *Am Ind Hyg Assoc J* 1979; 40(2):108-17.

Esmen NA, Sheehan MJ, Corn M, Engel M, Kotsko N. Exposure of employees to manmade vitreous fibers: installation of insulation materials. *Environ Res* 1982; 28(2):386-398.

Gardner MJ, Winter PD, Pannett B, Simpson MJ, Hamilton C, Acheson ED. Mortality Study of Workers in the Man-Made Mineral Fiber Production industry in the United Kingdom. *Scand J Work Environ Health* 1986; 12(suppl 1):85-93.

Gardner MJ, Magnani C, Pannett B, Fletcher AC, Winter PD. Lung cancer among glass fibre production workers: A case-control study. *Br J Ind Med* 1988; 45:613–618.

Greenland S. Dose-response and trend analysis in epidemiology: Alternatives to categorical analysis. *Epidemiology* 1995; 6:356-365.

Guber A, Lerman S, Lerman Y, Ganor E, Trajber I, Edelstein E, Fireman E. Pulmonary fibrosis in a patient with exposure to glass wool fibers. *American Journal of Industrial Medicine* 2006; 49:1066-1069.

Gustavsson P, Plato N, Axelson O, Brage HN, Hogstedt C, Ringback G, Tornling G,Wingren G. Lung cancer risk among workers exposed to man-made mineral fibers (MMMF) in the Swedish prefabricated house industry. *Am J Ind Med* 1992; 21:825–834.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 81. Man-Made Vitreous Fibers, Lyon, France, 2002.

Kjuus H, Skjaerven R, Langard S, Lien JT, Aamodt T. A case referent study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and exposure-based occupational information. *Scand J Work Environ Health* 1986a; 12:193–202.

Kjuus H, Skjaerven R, Langa°rd S, Lien JT, Aamodt T. A case referent study of lung cancer, occupational exposures and smoking. II. Role of asbestos exposure. *Scand J Work Environ Health* 1986b; 12:203–209.

Marchant GE, Amen MA, Bullock CH, Carter CM, Johnson KA, Reynolds JW. Connelly FR, Crane AE. A synthetic vitreous fiber (SVF) occupational exposure database: implementing the SVF health and safety partnership program. *Appl Occup Environ Hyg* 2002; 17:276-285.

Marsh GM, Stone RA,YoukAO, Smith TS, Quinn MM, Henderson VL, Schall LC, Wayne LA, Lee KY. 1996. Mortality among United States rock wool and slag wool workers: 1989 update. *Int J Occup Health Saf* 1996; 12:297–312.

Marsh GM, Youk AO, Stone RA, et al. Historical cohort study of U.S. man-made vitreous fiber production workers: I. 1992 fiber glass cohort follow-up: initial findings. *J Occ Environ Med* 2001a; 43:741-756.

Marsh GM, Gula MJ, Youk AO, Buchanich JM, Churg A, Colby TV. Historical cohort study of U.S. man-made vitreous fiber production workers: II. Mortality from mesothelioma. *J Occ Environ Med* 2001b; 43:757-766.

Marsh GM, Youk AO, Stone RA, et al. Historical cohort study of U.S. man-made vitreous fiber production workers: VI. Respiratory system cancer standardized mortality ratios adjusted for the confounding effect of cigarette smoking. *J Occ Environ Med* 2001c; 43:803-808.

Maxim LD, Eastes W, Hadley JG, Carter CM, Reynolds JW, Niebo R. Fiber glass and rock/slag wool exposures of professional and do-it-yourself installers. *Regulatory Toxicology and Pharmacology* 2003; 37:28-44.

Morgan RW, Kaplan SD, Brasberg JA. Mortality study of Fibrous Glass Production Workers. *Arch Environ Health* 1981; 36(4):179-83.

Pintos J, Parent M, Rousseau M, Case B, Siemiatycki J. Occupational Exposure to Asbestos and Man-Made Vitreous Fibers, and Risk of Lung Cancer: Evidence from Two Case-Control Studies in Montreal, Canada. *J Occ Environ Med* 2008; 50(11): 1273-1281.

Plato N, Westerholm P, Gustavsson P, Hemmingsson T, Hogstedt C, Krantz S. Cancer incidence, mortality and exposure-response among Swedish man-made vitreous fiber production workers. *Scand J Work Environ Hlth* 1995; 21:353-361.

Quinn MM, Smith TJ, Youk AO, et al. Historical cohort study of U.S. man-made vitreous viber production workers VIII. Exposure-specific job analysis. *J Occ Environ Med* 2001; 43:824-834.

Sali D, Boffetta P, Andersen A, Cherrie J, Claude J, Hansen J, et al. Non-neoplastic mortality of European workers who produce man made vitreous fibers. *Occup Environ Med* 1999; 56:612-617.

Shannon HS, Hayes M, Julian JA, Muir DCF. Mortality experience of glass fibre workers. *British Journal of Industrial Medicine* 1984; 41:35-38.

Shannon, H.S., Jamieson, E., Julian, J.A., Muir, D.C.F., Walsch, C. Mortality experience of glass fibre workers: extended follow-up. *Annals of Occupational Hygiene* 1987; 31:657-662.

Shannon HS, Jamieson E Julian JA, et al. Mortality of glass filament (textile) workers. *Br J Ind Med* 1990; 47:533-536.

Shannon HS, Muir A, Haines H, Verma D. Mortality and cancer incidence in Ontario glass fiber workers. *Occup Med* 2005; 55:528-534.

Simonato, L., Fletcher, A.C., Cherrie, J., et al. The man-made mineral fibres (MMMF) European historical cohort study: extension of the follow-up. *Annals of Occupational Hygiene* 1987; 31:603-623.

Smith TJ, Quinn MM, Marsh GM, et al. Historical cohort study of U.S. man-made vitreous fiber production workers: VII. Overview of an exposure assessment. *J Occ Environ Med* 2001; 43:809-823.

Stanton MF, Wrench C. Mechanisms of mesothelioma induction with asbestos and fibrous glass. *J Natl Cancer Inst* 1972; 48:797-821.

Stone RA, Youk AO, Marsh GM, Buchanich JM, McHenry MB, Smith TJ. Historical cohort study of U.S. man-made vitreous fiber production workers: IV. Quantitative Exposure-Response Analysis of the Nested Case-Control Study of Respiratory System Cancer. *J Occ Environ Med* 2001; 43:779-792.

Stone RA, Youk AO, Marsh GM, Buchanich JM, Smith TJ. Historical Cohort Study of US Man-Made Vitreous Fiber Production Workers IX: Summary of 1992 Mortality Follow Up and Analysis of Respiratory System Cancer Among Female Workers. *J Occ Environ Med* 2004; 46(1):55-67.

Watkins DK, Chiazze L, Jr., Fryar C. Historical cohort mortality study of a continuous filament fiberglass manufacturing plant. II. Women and minorities. *J Occup Environ Med* 1997; 39:548–555, 1997.

Weiderpass E, Vainio H, Kauppinen T, Vasama-Neuvonen K, Partanen T, Pukkala E. Occupational Exposures and Gastrointestinal Cancers Among Finnish Women. *J Occ Environ Med* 2003; 45(3): 305-315.

Wong, O., Foliart, D., Trent, L. A case-control study of lung cancer in a cohort of workers potentially exposed to slag wool fibers. *British Journal of Industrial Medicine* 1991; 48:818-824.

Youk AO, Marsh GM, Stone RA, Buchanich JM, Smith TJ. Historical cohort study of U.S. man-made vitreous fiber production workers: III Quantitative Exposure-Response Analysis of the Nested Case-Control Study of Respiratory System Cancer. *J Occ Environ Med* 2001; 43:767-778.